REC'D 28 JUN 2005
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT25572	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IT2004/000117	International filing date *(day/month/year)* 08.03.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC C12N15/11, A61K48/00		
Applicant GIULIANI S.p.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

CORRECTED VERSION

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2005	27.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zellner, E Telephone No. +49 89 2399-8427

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000117

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-27 as originally filed

Sequence listings part of the description, Pages

1-7 received on 11.05.2004 with letter of 08.03.2004

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1-5 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000117

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

V

1. Reference is made to the following documents:

   D1: MONTELEONE G ET AL: "BLOCKING SMAD7 RESTORES TGF-BETA1 SIGNALING IN CHRONIC INFLAMMATORY BOWEL DISEASE" JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 108, no. 4, August 2001 (2001-08), pages 601-609, XP001152527 ISSN: 0021-9738

   D2: US-A-6 159 697 (COWSERT LEX M ET AL) 12 December 2000 (2000-12-12)

   D3: KRIEG A M: "Mechanisms and applications of immune stimulatory CpG oligodeoxynucleotides" BIOCHIMICA ET BIOPHYSICA ACTA . GENE STRUCTURE AND EXPRESSION, ELSEVIER, AMSTERDAM, NL, vol. 1489, no. 1, 10 December 1999 (1999-12-10), pages 107-116, XP004275526 ISSN: 0167-4781

   D4: US 2002/034736 A1 (FALB DEAN A ET AL) 21 March 2002 (2002-03-21)

2. The closest prior art document D1 describes phosphorothioate oligonucleotides against Smad7 having the identical nucleotide sequence as disclosed in the present set of claims (D1 page 602, right column, lines 15-21).
   The authors demonstrate that blocking Smad7 with specific antisense oligonucleotides restores TGFβ1 signalling and allows TGF-β1 to inhibit proinflammatory cytokine production by isolated mucosal lamina propria mononuclear cells. In other words Smad7 inhibition enables endogenous TGF-β to downregulate the response in IBD (inflammatory bowel disease).
   In difference to the present application the nucleotide bases designated as X,Y or Z in the present application are not methylated in D1. As mentioned in the description of the present application the antisense oligonucleotides of D1 have an increased risk of undesirable side effects (page 6, lines 29-33) and in addition an effective in vivo inhibition being higher that the in vitro inhibition (page 22 Table 4 in the present application).
   The problem is thus defined as the provision of less toxic oligonucleotides blocking Smad7 effectively.
   The problem is solved by the selection of a particular antisense oligonucleotides and the methylation of the particular sites such as X,Y (being originally CG in D1) and Z such as defined in the present set of claims.

Said solution is considered to involve an inventive step for the following reasons. D2, suggests modified nucleobases such as 5-methylcytosine for antisense phosphorothioate oligonucleotides against Smad7 (column 40 - 42). D3 also suggests the methylation of CG motifs in antisense oligonucleotides, in order to have less side effects. In D4 methylphosphonate oligonucleotides against Smad7 are described (page 25, [0243 and 0245, 403]). However D2 and D4 select different antisense target sequences.
From D1 it could not be expected that selecting a particular antisense being identical in its base sequence to the one of the present application and methylating particular bases would result in a higher in vivo effect than in vitro such as demonstrated in Table 4 of the present application.

In consequence, the present set of claims are novel and inventive (Article 33(2) (3) PCT).

VIII

1. The wording "portion of at least 10 nucleotides" is not clear, as all the antisense nucleotides of Table 4 are loner that 10 nucleotides. Thus, there is no sufficient disclosure for less that the nucleotides shown in Table 4 (Article 5 and 6 PCT)

2. Claim 14 is not clear (Art. 6 EPC) as no particular disease is specified in said claim.